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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,565	GODDARD ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/21/05 6/20/05 8/24/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/1/05, 6/6/05, 6/20/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.D

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 21 March 2005, 20 June 2005, and 24 August 2005 have been entered.

4. Claims 1 – 4 are cancelled; claims 5 – 20 are pending and under examination.

Priority

5. The preliminary amendment filed 12 September 2002 indicates that this application is a continuation of application 10/006867, which is a continuation of PCT/US00/23328, which is a continuation-in-part of application 09/390137, which is the national stage entry of PCT/US99/12252, which claims benefit of 60/088734. The instant disclosure receives priority to 24 August 2000, the earliest application in which the specification was identical. Priority is not granted to earlier applications because the disclosure is not enabling.

It is noted that applicants may argue that the results of the assay beginning on page 140 (paragraph 529) of the specification, the Tumor versus Normal Differential Tissue Expression Distribution assay, establish utility and enablement for the claimed invention, resulting in an earlier priority date. That assay is found to be lacking utility and therefore is not found to be enabling as required by 35 U.S.C. § 112, first paragraph for reasons made of record in the office actions mailed 17 May and 20 October 2004 and reiterated below.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration, particularly changes to the address of inventor Eaton. See 37 CFR 1.52(c).

Claim Rejections - 35 USC §§ 101 and 112

7. Claims 5 – 20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 5 – 13 had previously been rejected under 35 USC 101 for lacking a specific and substantial or well-established utility. This rejection is maintained for the reasons of record and explained in further detail below. New claims 14 – 20 are rejected for the same reasons.

Briefly, the previously-presented claims were rejected because the specification did not show how to use the instantly-claimed proteins. The specification provided only a single example wherein a small fragment of a nucleic acid encoding the instantly-claimed SEQ ID NO:58 is more highly expressed in esophageal tumor than in normal esophagus. The nucleic acid that was used in this experiment was not the entire sequence of SEQ ID NO:57, but rather a fragment approximately 200 – 600 bp long (see specification p. 140), of undisclosed sequence and undisclosed location on SEQ ID NO:57. There is no disclosure of any use for instantly-claimed SEQ ID NO:58, and furthermore there is no disclosure of any evidence of utility for a nucleic acid that encodes SEQ ID NO:58.

On p. 7 of the remarks filed 21 March 2005, applicant argues that the data presented are sufficient to meet the legal standard for utility. Applicant's arguments have been fully considered but are not deemed persuasive.

Applicant cites *Brenner v. Manson* as support for the argument that a patent should be granted for useful inventions. Applicant provides a quotation of a single sentence, which has been removed from its context. In fact, the very next sentence from *Brenner* states that "Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Further on, the court reasoned that "This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short

of the invention of something "useful," or that we are blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy. " (citations omitted). In the instant case, applicant's claimed invention is not useful in its currently available form because the specification does not disclose how to use the instantly-claimed SEQ ID NO:58, or variants related by percentage identity which have certain properties. Thus following the logic of the *Brenner* court, there is insufficient justification for awarding a patent.

Applicant also cites MPEP § 2107.01 which states that "any reasonable use that an applicant has identified for the invention can be viewed as providing a public benefit should be accepted as sufficient" (emphasis added). Applicant argues that it is reasonable to expect that the instantly-claimed protein is useful as a diagnostic or a therapeutic because a small fragment of a nucleic acid which encodes it is more highly expressed in esophageal tumor than in normal esophagus. This is not a reasonable use. The art cited by applicant on the IDS filed 6 June 2005 is particularly informative. Chen (2002. Molecular and Cellular Proteomics 1.4:304-313) teaches that there is not a statistically significant correlation between mRNA and protein expression. Haynes (1998. Electrophoresis 14:1862-1871) provides similar teachings; mRNA expression levels can vary by up to 40-fold without a change in protein levels. Thus, it is not reasonable to assert utilities for proteins when the only evidence of record is drawn to expression of nucleic acid.

Applicant also cites MPEP § 2107 II(B)(1) on p. 7 of the remarks. The text from MPEP cited by applicant is not relevant here. The text tells the examiner not to impose a rejection based on lack of utility if applicant's "assertion would be considered credible by a person of ordinary skill in the art". The instant claims have not been rejected for lack of a credible utility, but rather for lack of specific and substantial utility. Applicant also cites MPEP § 2107.02 (VII) on p. 8 of the remarks. Applicant argues that utility should be acknowledged for the instantly-claimed proteins, because that should be done when the evidence, considered as whole, leads a person of ordinary skill in the art to conclude that the asserted utility is more likely true than not. In the instant case, the evidence of record taken as a whole do not lead the artisan of ordinary skill to such a conclusion. The only data presented in the specification which are on topic are those of Example 18. These are data on the expression of nucleic acids. The

evidence of record indicates that this is not a reasonable surrogate for data on expression of proteins, which are claimed herein.

Beginning on p. 8 of the remarks, applicant argues that utility need not be proven, that a reasonable correlation between the evidence and the asserted utility is sufficient, and that the guidance provided in MPEP § 2107.02 VII indicates that the asserted utility should be accepted if it is more likely than not true. Applicant cites *In re Langer*, *In re Jolles*, *In re Irons*, *In re Sichert*, *Raytheon v. Roper*, and *In re Oetiker* as supporting this argument. Applicant's arguments have been fully considered but are not persuasive.

In the instant case, applicant has asserted that the protein of SEQ ID NO:58 have utility because it can be used to diagnose cancer. On p. 140-144 of the specification there is a table which indicates that a small fragment of a nucleic acid which encodes SEQ ID NO:58 is more highly expressed in esophageal tumor than in normal esophagous. Again, the data presented are on nucleic acid levels, but applicant is not claiming nucleic acids; applicant is claiming protein. Because the correlation between expression of the nucleic acid and the protein is poor, data as to the expression of nucleic acids do not bear on the utility of proteins. Clearly, further research and experimentation are required to find out whether SEQ ID NO:58 or proteins which are at least 95% identical to it are useful as asserted, particularly as the nucleic acid sequence used was from an undisclosed portion of SEQ ID NO:57, and are not indicative of changes in the full-length protein SEQ ID NO:58.

In *In re Langer*, the court ruled the Patent Office cannot require clinical testing in humans to rebut a prima facie case for lack of utility. In the instant case, the Office has not made such a requirement. Furthermore the Langer court ruled that "Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." In the instant case there is in fact sufficient reason to question the statement of utility. The instantly-claimed proteins are not clearly useful as either diagnostics or therapeutics for cancer, because there is not evidence of a correlation between the expression level of the protein and the presence or absence of a tumor.

In *In re Jolles*, the issue was whether data from an art-recognized animal model could be considered predictive of results in humans. That is not an issue in the instant case, as the data presented on pp. 140 – 144 of the specification are from human tissue samples. If there were a

correlation between the expression level of SEQ ID NO:58 and the presence of cancer, there might be a patentable utility for the protein. However, since there is not evidence of such a correlation applicant's arguments do not seem to be on point.

The citation of *In re Irons* is also not relevant to the instant case. In *Irons*, evidence was submitted that indicated that the drug had been administered to 888 patients and that statistically significant results were obtained showing an improvement in arthritic conditions. In the instant case, no such evidence has been submitted. The only data of record are drawn to the nucleic acid, but the instant claims are drawn to protein. Furthermore, there is no evidence of record indicating a statistically significant result at either the nucleic acid or the protein level.

The *Sichert* court ruled that blind comparative studies of the claimed compositions, which showed that the compositions were effective in relieving lymphatic congestion (as narrowly defined), were sufficient to establish utility of said compositions under 35 USC § 101. In the instant case, applicant has not shown any such studies, and therefore because the fact pattern is sufficiently different the *Sichert* case is not germane.

In *Raytheon v. Roper*, utility was found by the Federal Circuit when a lack of utility had been found by a lower court. This was due not to the sufficiency of the evidence presented, but rather because the Federal Circuit ruled that the claims in question had been interpreted erroneously. In the instant case, there does not appear to be a question as to how the pending claims are being interpreted. Rather, utility is found to be lacking because there is not a correlation between SEQ ID NO:58 expression and the presence or absence of cancer.

It is not immediately apparent why applicant has cited *In re Oetiker* in arguments related to the utility under 35 USC § 101, as the *Oetiker* case dealt not with utility but with obviousness under 35 USC § 103. No claims were rejected under § 103 in the Final Rejection mailed 20 October 2004.

Applicant also cites *In re Brana*, wherein it was pointed out the PTO has the initial burden to offer evidence that one of ordinary skill would doubt the asserted utility. In fact, on p. 4 of the office action mailed 17 May 2004, the examiner quite clearly indicated that "further research would be required to determine how and if PRO 1106 is involved in any disease", because the data presented were at the level of nucleic acid, and as set forth in the preceding paragraphs is not necessarily correlated with protein expression or activity. No rebuttal evidence has been presented, therefore whether or not said evidence is reasonably indicative of the asserted utility is not refuted. This argument is reiterated on p. 18 of the remarks and is

deemed not persuasive for the same reasons: no rebuttal evidence drawn to the utility of the instantly-claimed protein has been presented.

In *Fujikawa v. Wattanasin*, the court ruled that test results need not absolutely prove the asserted utility, and that presentation of relevant results from an *in vitro* model system may be sufficient to provide utility. However the instant case varies in an important manner from the *Fujikawa* case. In *Fujikawa*, there were data of record as to the utility of the compound that was the subject of the case. In the instant case, applicant has not provided any in vitro data as to the utility of the invention SEQ ID NO:58. Thus the court's findings in *Fujikawa* are not relevant, as the facts are not analogous to those of the earlier case.

On p. 9 of the remarks, applicant cites *Cross v. Iizuka*. As applicant indicates, the *Cross* court ruled that *in vitro* tests could be predictive of in vivo results and if an appropriate in vitro test is used that may be sufficient to confer utility under 35 USC 101. However, as pointed out previously, the specification does not disclose the results of any tests, *in vitro* or *in vivo*, that support the utility of SEQ ID NO:58.

In summary, applicant's arguments that absolute proof is not necessary, and that a reasonable correlation between the evidence presented and the asserted utility should be sufficient to give utility to the claimed invention do not carry weight. This is because there is not evidence of a correlation between the presence or absence of SEQ ID NO:58 and cancer.

On p. 11 of the remarks applicant refers to the declaration of record by Dr. Grimaldi. This declaration was considered and not found persuasive in the previous office action (see the paragraph spanning pp. 3 – 4 of the office action mailed 20 October 2004). However applicant again directs the examiner's attention to the declaration. On p. 16 of the remarks, applicant refers to the declaration by Grimaldi (exhibit A) in which the importance of the data in Example 18 are explained.

The declaration (exhibit A) under 37 CFR 1.132 filed 18 August 2004 is insufficient to overcome the rejection of previously rejected claims 5 – 13 and new claims 14 – 20 based upon lack of utility as set forth in the last Office action because:

1) The declaration is not commensurate in scope with the claims. The claims are drawn to SEQ ID NO:58, which is a polypeptide encoded by SEQ ID NO:57. The specification (page 140, paragraph 530) indicates that oligonucleotide probes were designed to amplify a portion of the DNA. The declaration indicates (paragraph 6) that using PCR, relative expression levels were scored for the fragments analyzed. Clearly, what was analyzed was the expression level

of a part of SEQ ID NO:57, not the entire sequence. Furthermore, the fragment which was analyzed is not identified either in the specification or the declaration. The data presented are narrow, in that they deal with a fragment of SEQ ID NO:57 200 – 600 bp in length. In contrast, the claims are drawn to a different invention, i.e. to full-length protein of SEQ ID NO:58 or fragments or variants thereof.

2) The data presented are subjective in nature and not objective. Paragraph 6 of the declaration indicates that expression levels were assigned one of three values: +,-, or +/-. There is no indication how the expression levels were scored, nor is there any indication of what differentiates either a + or – sample from an intermediate (+/-) sample. Additionally, there is no indication that the data are repeatable, as the experiments seem to have been performed once on a single sample. Furthermore, because there is no indication that the differences observed are statistically significant, it appears likely that the variability seen is not significant and would be expected by random variation alone. In paragraph 7 of the declaration, Dr. Grimaldi states that the nucleic acids are useful in detection of cancer. But the instant claims are drawn to protein, not nucleic acid. Applicant concludes that there is a two-fold difference in expression level (remarks, p. 16, final complete paragraph) but there are not sufficient facts in the record to support such a conclusion. The declaration states that a visible change on an ethidium bromide-stained agarose gel is sufficient to support the conclusion that a two-fold difference in cDNA expression. But this is not supported by sufficient facts, such as presentation of a standard curve which correlates expression level to staining intensity and corrects for length of nucleotide, as longer pieces of nucleic acid will have more ethidium bromide staining. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412, cited by applicant on IDS filed 6 June 2005) analyzed 2286 genes that showed a greater than I-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Additionally, the reference by Tokunaga et al. (2000. J Exp Clin Cancer Res 19:375-381) teaches that qualitative analysis of gene expression

in cancer tissue using RT-PCR is not sufficient, rather quantitative analysis must also be used. Additionally Tokunaga teaches that for clinical applications (i.e. the diagnostic utility of the instantly-claimed nucleic acid) much further research is needed (see final sentence of abstract). Finally, Chen et al. (2002. Molecular and Cellular Proteomics 1.4pp. 304-313, cited on IDS filed 6 June 2005) teach that of 165 nucleic acid-protein pairs examined, only a small subset showed a significant correlation and that overall there is not a significant correlation between gene expression and protein expression in cancer.

3) The actual data were not submitted in the declaration, rather a description of how the data were scored was submitted. The magnitude of the differences cannot be evaluated because the data were not submitted.

On p. 14 of the remarks filed 21 March 2005 applicant refers to the second declaration by Dr. Grimaldi (exhibit B filed 18 August 2004). The declaration (exhibit B) under 37 CFR 1.132 filed 18 June 2004 is insufficient to overcome the rejection of claims 4 – 13 and new claims 14 - 20 based upon lack of utility as set forth in the last Office action because:

The facts presented are not germane to the rejection at issue. In paragraph 5, Dr. Grimaldi asserts that there are often correlations between expression of nucleic acid and of protein. The specification discloses that there are certain changes in expression of an unspecified fragment of SEQ ID NO:57 in some forms of cancer. As mentioned above, the teachings of Hu et al. indicate that subtle differences in gene expression are to be interpreted with great caution, and Haynes et al. teach there is not a strong correlation between gene expression at the level of nucleic acid and at the level of protein. Since the present claims are drawn to the protein, and the only data provided are on a fragment of a nucleic acid sequence, the statements are not on point.

At p. 15, Applicant presents a declaration by Dr. Polakis filed 18 August 2004 under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are

predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive.

The declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. The declaration is not on point to the claimed sequence as it does not state that these successes are in using cancer diagnostics with the instantly-claimed sequences. The evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide is not on point to the instantly-claimed protein. There is no evidence provided in the declaration that there is a correlation between mRNA levels and protein expression for SEQ ID NO:58. In fact, the references by Haynes and Chen cited above show that mRNA expression level is not well correlated with protein expression level.

Furthermore, the text from applicant's exhibit 1, p. 453, cited by applicant on p. 20 of the remarks clearly indicates that other controls can act later in the pathway from RNA to protein. Applicant also presents arguments from newly submitted exhibits 1 – 2 and articles by Zhang and Meric previously submitted in support of the arguments for utility. The arguments from exhibits 1 – 2 and the article by Zhang are concerned with the correlation between mRNA levels and protein levels. Exhibits 1 and 2 discuss regulation of genes in general but are not on point to the specific protein at issue here i.e. SEQ ID NO:58. The article by Zhang is drawn to a specific protein, namely PSCA, but is not germane because the claims are not directed to either PSCA; they are drawn to antibodies which bind to a different, unrelated protein. The argument from the article by Meric et al. is that differences in gene expression between normal and cancer cells makes those genes targets for therapeutics. However this article is not on point to the instantly-claimed protein, SEQ ID NO:58. In fact, the next sentence in the paragraph of Meric cited by applicant is directly on point "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." Thus the paragraph presented by applicant, taken in its entirety, suggests that it is not proper to conclude that there are changes in protein level when changes in the mRNA level are observed.

In the paragraph bridging pp. 16 – 17 of the remarks applicant argues that it is irrelevant whether or not the changes in mRNA seen in the small fragment of SEQ ID NO:57 are due to aneuoploidy or changes in the rate of transcription, and that since the specification provides

relaible evidence that PRO 1106 mRNA is differentially expressed in certain tumors utility should be acknowledged. The examiner disagrees. There is insufficient evidence of record to support the premise of applicant's argument, that the specification provides reliable evidence that PRO 1106 mRNA is differentially regulated. Furthermore the examiner has provided ample evidence that there is not a reliable correltation between gene expression at the level of nucleic acid and the amount of protein observed. Applicant has not provided any evidence that the instantly-claimed protein is in fact differentially regulated in cancers.

On p. 18 of the remarks, applicant again cites the court's decisions in *In re Langer* and *In re Oetiker*. The facts of the instant case are different from those cases; they have been discussed in more detail on pp. 5 – 6 of this office action. On p. 19 of the remarks applicant argues that the asserted utility for the claimed protein is specific, in that it is related to a specific disease or condition. The examiner agrees, however the standard for utility is that it must be specific and substantial (see MPEP § 2107.01), and since the utility is not substantial for the reasons made of record previously and reiterated above, the claimed invention does not satisfy the "useful" requirement of 35 U.S.C. 101. Thus the rejection of the previously presented claims stands and applies to the newly-presented claims as well.

8. Claims 5 – 20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Even if utility were shown for claims 5 – 6, 9 – 10, 12 - 20, they would remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for proteins less than 100% identical to SEQ ID NO:58 wherein the nucleic acid which encodes the protein is more highly expressed in esophageal tumor than in normal esophagus tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6)

breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

As stated in the office action mailed 17 May 2004, applicant has not disclosed any sequences less than 100% identical to SEQ ID NO:58. The specification does not provide guidance as to which regions of the protein are required for the activities recited in claims 5, 14 – 16, or 19. Claims 14 – 16, for example recite the limitation that the polypeptide can be used to make an antibody which can detect the differential expression of the protein in tumor or normal esophageal cells. Any six amino acids could be used to make an antibody to the instantly-claimed protein (see Hopp et al. 1981 PNAS 78:3824 – 3828), and applicant has not shown which regions of the protein must be preserved for the proper antibodies to be made. Furthermore there is no disclosure of the protein being differentially expressed. Claim 5 requires that the protein is encoded by a nucleic acid that is more highly expressed in esophageal tumor than in normal esophagus. As stated in the first full paragraph of p. 5 of the office action mailed 20 October 2004, this is not a functional limitation of the polypeptide, as the function of a polypeptide is not reasonably related to the expression pattern of a nucleic acid. Thus there is not a nexus between the functional limitation and the percent identity limitations recited in claim 5. Claims 19 – 20 require that the claimed variants of SEQ ID NO:58 be more highly expressed in esophageal tumor than in normal esophagus, or be encoded by a nucleic acid which has this pattern. The nucleic acid limitation is addressed earlier in this paragraph. There is no disclosure of a protein related to SEQ ID NO:58, or even of SEQ ID NO:58 itself, having the recited expression pattern. Applicant has not provided guidance as to which regions of the protein must be retained, or which can be changed, in order for the protein to have the recited expression pattern. Thus the artisan would essentially have to resort to trial-and-error experimentation in order make the variants with the recited properties.

Claims 5 – 6, 11 – 20 are drawn to "the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209963". While the specification discloses the deposited cDNA sequence, there is no indication of which nucleotides comprise the full-length coding sequence. Thus the artisan would have to discover this sequence himself. Claims 5 – 6, 9 – 10, 12 – 20 are drawn to the extracellular domain of the protein. Figure 58 indicates that there are three putative transmembrane domains, but there is no indication of whether the N- or C-terminus of the

protein is intracellular or extracellular. If the N-terminus is intracellular, then the regions from residues 305 – 338 and from 395 to the C-terminus would be extracellular. If the N-terminus is extracellular, then the regions from residues 1 – 283 and 361 – 375 would be extracellular. Since the specification has not provided guidance as to which regions of the protein are extracellular the artisan would have to discover this region himself. Requiring this degree of experimentation is undue given the large degree of experimentation required and the paucity of guidance provided by the specification.

Applicant argues, on p. 21 of the remarks, that the claims are related to polypeptides at least 99% identical to SEQ ID NO:58. However claim 5 as amended recites 95% identity. Applicant argues that making and testing variants is within the skill of the artisan. However given the enormous amount of testing that the artisan would have to undertake (i.e. the artisan would have to discover whether or not the claimed polypeptide is overexpressed in esophageal tumors, would have to discover the regions which must be retain so the antibodies generated from the protein detect such a difference, and would have to discover the regions of the nucleic acids which encode the protein must be retained such that the proteins have the proper expression pattern) and the paucity of guidance provided in the specification and the fact that there are no working examples of proteins less than 100% identical to instantly-disclosed SEQ ID NO:58, such experimentation would be undue.

10. Claims 5 – 6, 11 – 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R § 1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 209963 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years and *at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.* See 37 C.F.R. § 1.806.

11. Claims 5 – 6, 9 – 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant argues, on p. 23 of the remarks, that the legal standard for the description requirement can be found in *In re Kaslow*, *Vas-Cath*, and *Union Oil*. The examiner agrees that these case provide the basis of the requirement. Applicant argues, on p. 23 of the remarks, that the claims are related polypeptides at least 99% identical to SEQ ID NO:58. However claim 5 as amended recites 95% identity. Applicant argues that there is not substantial variation in the peptides at least 99% identical to SEQ ID NO:58. First, several claims are drawn to peptides at least 95%, not 99%, identical (see claim 5 and dependent claims 12 – 13). Applicant point the examiner to Example 14 of the written description training materials as providing support for the argument that claims to proteins at least 99% identical to the disclosed sequence with an appropriate functional limitation are deemed to meet the description requirement. However that example is drawn to an enzyme. Enzymes are a sub-genus of proteins; and it is generally known which structures are common to enzymes and thus must be preserved (for instance, an ATP-binding domain must be preserved for a kinase to transfer a phosphate to its substrate). The instantly-disclosed SEQ ID NO:58 is not disclosed as being an enzyme and thus Example 14 is not on point. Applicant is directed to the the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at http://www.uspto.gov/web/offices/pac/writtendesc.pdf, which is analogous to the instant situation. Independent claims 5, 14 – 16, and 19 – 20 are genus claims, but neither the art nor the specification discloses a representative number of species falling within the genus. There is not even identification of any particular portion of the structure at either the nucleic acid or amino acid level that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Additionally, the extracellular domain has not been identified in the specification. Figure 58 discloses that there are three predicted transmembrane domains but there is no disclosure of which end of the protein is intracellular or extracellular. Furthermore, there is no identification of which parts of the nucleic acid sequence deposited with ATCC are the full-length coding sequence. Therefore claims which recite either the full-length coding sequence of the cDNA

deposited with ATCC or the extracellular domain do not meet the written description requirement.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 5 – 6, 9 – 10, 12 – 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims which recite "the extracellular domain" are indefinite. There is no disclosure of which end of the protein is the extracellular end. Figure 58 discloses that there are three transmembrane domains. If the N-terminus is intracellular, then the regions from residues 305 – 338 and from 395 to the C-terminus would be extracellular. If the N-terminus is extracellular, then the regions from residues 1 – 283 and 361 – 375 would be extracellular. Because the artisan cannot determine which regions of the protein are extracellular, he cannot determine the metes and bounds of the claims.

Claim 10 recites "the extracellular domain of the polypeptide of SEQ ID NO:58, lacking its associated signal peptide." This is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell (see Alberts et al. 1994. Molecular Biology of the Cell p. 582).

Claim Rejections - 35 USC §§ 102 and 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 5 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative obvious over, either Strachan (U.S. Patent 6,573,095, cited in office action mailed 17 May 2004) or Strachan et al. (U.S. Patent 6,150,502, issued 21 November 2000, filed 9 November 1998). The '095 patent issued from an application which is a continuation-in-part of the application which was the basis of the '502 patent. The sequence is disclosed in both patents. Strachan teaches SEQ ID NO:339, which is 97.5% identical to applicant's SEQ ID NO:58. The prior art sequence meets the structural limitation recited in claim 5, part (a) and claim 14, part (a). The examiner cannot determine if the sequence has the properties recited at the end of the claims, but since it meets the structural limitation rejection under either 35 USC 102 or 103 is proper.

Applicant refers to the declaration submitted by Goddard et al. as providing evidence that he was in possession of the claimed invention before the effective filing date of the above-cited patents. The declaration by Goddard filed on 21 March 2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Strachan references. The declaration is not on point to the claimed invention. The declaration provides evidence that applicant was in possession of the amino acid sequence of SEQ ID NO:58 prior to 29 April 1998. However, claims 5 and 14 are drawn to polypeptides 95% identical to SEQ ID NO:58 which have certain properties. The declaration does not provide evidence that applicant was in possession of the polypeptides related by sequence identity which have the recited properties. For the reasons stated above the declaration fails to overcome the rejection.

16. Claims 5, 12 – 13, 14, and 17 – 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of the Strachan patents (6,573,095 or 6,150,502), in view of Lo (1998. Protein Engineering 11:495-500). Both Strachan patents teach SEQ ID NO:339, which is 97.5% identical to applicant's SEQ ID NO:58. Neither patent teaches this sequence fused to an Fc region.

Lo et al. teach fusing a nucleic acid sequence encoding essentially any mammalian protein can be fused to immunoglobulin Fc region (p. 495, paragraph spanning the two columns). Lo et al. also teach this is advantageous as it allows rapid production and purification of gene products, which is necessary to identify and understand their functions (p. 495, second

paragraph). Furthermore Lo et al. teach that their method is particularly useful as it allows for increased quantities of the proteins, with the advantage that they are secreted in the culture medium (p. 499, Discussion, first paragraph), allowing easy recovery. It would have been obvious to one of ordinary skill in the art to create a fusion protein comprised of Strachan's SEQ ID NO:339 and Fc, with a reasonable expectation of success. The motivation would be to rapidly produce the protein at high purity, as taught by Lo et al.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
August 29, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
8-31-05